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Prevalence of Oral Lesions and Periodontal Diseases in HIV-infected Patients on Antiretroviral Therapy

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Abstract: A cross-sectional study examining oral manifestations was carried out in HIV-infected patients of a general HIV-specialized unit to provide prevalence data on oral lesions and periodontal diseases. The occurrence of oral lesions was correlated with demographic and clinical characteristics, immunologic and virologic parameters.

Among 139 patients 86% presented any oral lesions with a prevalence of 76% of any periodontal diseases. Most periodontal lesions were classified as conventional gingivitis (28%) or periodontitis (30%). Dental plaque formation was associated with a higher prevalence of periodontal diseases ($p = 0.01$) and periodontal inflammation scores were higher in patients with more reduced CD4-counts ($p = 0.03$). Prevalence for HIV-specific oral lesions was 29% with a proportion of 9% of linear gingival erythema (LGE), 3.6% of necrotizing and ulcerative gingivitis (NUG) or periodontitis (NUP), 7% of oral candidiasis, 3.6% of oral hairy leucoplakia (OHL) and single other lesions. HIV-specific lesions (NUG/NUP, oral candidiasis and OHL) were found predominantly in patients with advanced immunosuppression and elevated viral load.

Compared with data of oral diseases of the pre-HAART era prevalence of HIV-specific lesions was markedly reduced. Especially frequently known lesions such as oral candidiasis and OHL were less common seen. We noticed a shift of prevalence towards periodontal diseases. Lack of oral hygiene determined by plaque formation and reduced CD4-counts with pronounced periodontal inflammation can be seen as risk factors for periodontal disease. Overall high prevalence of manifestations underlines the importance of oral examination for the general practitioner and visits by oral specialists should become a routine procedure in HIV-patients care.

Key words: HIV, HAART, periodontal disease

Introduction

Since the beginning of the AIDS epidemic oral manifestations have been a hallmark of the immunodeficiency syndrome. In previous studies about 40% of all HIV-infected individuals showed one or more HIV-associated oral manifestations, and these rates increased to over 90% by the time patients reach the late stages of immunosuppression of this disease [1-6]. Candidiasis and oral hairy leucoplakia (OHL) were the most common oral lesions found in HIV with a prevalence ranging from 12% to 54% for candidiasis, and from 5% to 20% for hairy leucoplakia. A strong association between these lesions and declining CD4+ T cells as well as AIDS defining illness have been shown [4]. Periodontal diseases are another common oral manifestation in HIV and are classified according to EC-Clearinghouse on Oral Problems Related to HIV Infection and WHO-Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus 1993 [7]. The classification consists of the linear gingival erythema (LGE), necrotizing ulcerative gingivostomatitis (NUG) and necrotizing ulcerative periodontitis (NUP) which have to be differentiated from more common periodontal conditions such as chronic adult periodontitis and acute gingivitis. General HIV practitioners might be less familiar with periodontal manifestations in HIV disease, although these lesions have been shown to be indicative for HIV disease progression as an associated with different levels of immunosuppression have been described. Several studies support the notion that the linear gingival erythema (LGE), characterized by a marginal band of intense erythema with a more apical focal and/or diffuse areas of erythema, is associated with earlier stages of HIV infection and CD4 suppression. It is often associated with pain and bleeding stigmata. On the other hand necrotizing ulcerative periodontitis (NUP), characterized by marginal necrosis of the gingiva and rapid destruction of the alveolar bone with further loss of attachment is a strong predictor of a more pronounced CD4 cell depletion [4, 8]. There is evidence that the linear gingival erythema is a precursor of the necrotizing ulcerative periodontitis as the microbiological environment found in both diseases were similar [9, 10]. The microbiological profile includes most of the flora seen in chronic adult periodontitis. In addition, there were several opportunistic microbes seen in HIV positive patients. Of particular interest is the high prevalence of Candida albicans as its invasion into the soft tissue is closely associated with periodontal disease [11]. Of importance are findings, that more common periodontal diseases can be as well associated with declining CD4 counts. Acute necrotizing ulcerative gingivostomatitis in HIV patients had fewer known classic risk factors such as poor oral

hygiene and inadequate sleep than in HIV negative individuals [12]. The acute necrotizing ulcerative gingivostomatitis (NUG) is characterized by necrosis of the interdental papilla and marginal ginigiva and may lead to severe interdental destruction. The involved area is often covered by removable pseudomembranes and disease may be accompanied with fever and local lymphadenopathia [13]. Since the beginning of highly active antiretroviral therapy (HAART) the prevalence of opportunistic infections has changed. Little is known about the prevalence of oral lesions in a population predominantly treated with HAART. Thus, the purpose of this study was to investigate the prevalence of oral lesions in an unselected subset of patients mainly treated with HAART at a general HIV-specialized unit.

Methods

Study population: Within a cross-sectional study 139 patients with chronic HIV-1 infection were enrolled at the HIV-out-patient-unit of the University Clinic of Düsseldorf during July 2000 – September 2001. Individuals were randomly asked to participate in the study and did not especially present oral symptoms during the time of inclusion. Exclusion criteria were known oral malignancy and former radiation. Patients were classified according to age, gender, ethnic origine, smoking habits and antiretroviral therapy. HIV status was evaluated according to CDC-classification, CD4+ T-cell count and HIV load. To assess immunologic and virologic parameters patients were grouped for CD4-count: <200cells/µl, 200-500cell/µl and >500 cells/µl and HIV-RNA: <1000 copies/ml and >1.000 copies/ml.

Dental examinations: Patients were examined by a dentist of the Dental Department of the University of Düsseldorf during their routine HIV check-up. Pathologic oral manifestations were classified according to EC-Clearinghouse on Oral Problems Related to HIV Infection and WHO-Collaborating Centre on Oral Manifestations of the Immunodeficiency Virus 1993 [7]. For the evaluation of the gingivo-periodontal manifestations hygienic and inflammatory indices were used. Microbiotic plaques are causative for gingivitis and periodontitis, therefore the Löe and Sillness gingival plaque-index (PI) was used to describe the number and intensity of plaques in interdental spaces and gingival ulcers.

Plaque-score	**manifestation**
grade 0	no plaques
grade 1	plaques only seen with a probe
grade 2	continues plaques at the sulcus gingivae, not involving the approximal space
grade 3	distinct plaques involving the interdental spaces

Löe and Sillness gingival plaque-index (PI)

$$\text{Calculation of Plaque-index (PI)} = \frac{\text{Total of plaque-scores}}{\text{Number of plaques}}$$

The Saxer and Mühlemann papillary-bleeding-index (PBI) describes the grade of inflammation of the periodontal gingiva after examination with a probe and application of moderate pressure.

Grade of bleeding	**Symptom (PBI)**
grade 0	healthy appearance, no bleeding after probe examination
grade 1	healthy appearance, but bleeding after probe examination
grade 2	bleeding after probe examination and inflammatory erythema
grade 3	bleeding after probe examination and inflammatory erythema with swelling
grade 4	bleeding after probe examination and inflammatory erythema with swelling and ulceration

Saxer and Mühlemann papillary-bleeding-index (PBI)

Statistical analysis: The statistical analysis was performed using SPSS (release 12.1). Chi-square test was used for univariate comparisons. P-values <0,05 were considered significant.

Results

139 patients consented and were enrolled in the study. The demographic and clinical characteristics of patients are presented in Table 1. Over 70% of patients had a CD4+ lymphocyte count > 200 cells/µl with 43% of these patients having a suppressed viral load <50 copies/ml with ART. Overall 129 (93%) patients were treated with ART (128 patients on triple-therapy, 1 patient on mono-therapy).

The prevalence of any pathological oral manifestations was 86 % (119 patients). The variety of oral manifestations is listed in Table 2. There was a prevalence

Table 1. Baseline characteristics.

Characateristics	**Patients n = 139**
Mean age in years (range)	34 (25-70)
Gender	
- Male	119 (86%)
- Female	20 (14%)
Ethnie	
-Caucasian	118 (85%)
- African	20 (14%)
- Asian	1 (1%)
CD4+ lymphocytes (cells/µl)	
- <200	38 (28%)
- 200-500	59 (43%)
- >500	39 (29%)
HIV-RNA (copies/ml):	
< 50 copies/ml	61 (45%)
> 50 copies/ml	75 (55%)
Patients with HAART	129 (93%)
Patients smoking	55 (40.3%)

Table 2. Characteristics and number of oral manifestation.

Oral manifestation	Number of cases (%)
Acute gingivitis	39 (28.1
Chronic periodontitis	42 (30.2)
- former ANUG/ANUP	6 (4.3)
Acute necrotizing ulcerative gingivitis (ANUG)	2 (1.4)
Acute necrotizing ulcerative periodontitis (ANUP)	3 (2.2)
Lineal gingival erythema (LGE)	13 (9.4)
Oral candidiasis	10 (7.2)
Oral hairy leucoplakia (OHL)	5 (3.6)
Kaposi`s sarkoma	1 (0.7)
Aphthous ulcers	2 (1.4)
Condylomata accuminata	2 (1.4)
Herpes simplex	4 (2.9)
Herpangina	1 (0.7)
ART-associated hyperpigmentation	2 (1.4)
Lues with oral manifestation	1 (0.7)
M. Osler	1 (0.7)
Bucal leucoplakia (e.g. nicotinica)	5 (3.6)
Oral fibroma	1 (0.7)
Epulis	1 (0.7)
Carcinoma of pallade	1 (0.7)

for periodontal manifestations in 76% (106 patients) and the most frequently seen periodontal lesions were acute gingivitis (bleeding after probe examination) in 28% (39 patients) and chronic periodontitis (profound pocket depth) in 30% (42 patients). In 6 out of 42 individuals with chronic periodontitis a former necrotizing and ulcerative gingivitis or periodontitis with interdental destruction was assumed. We found a prevalence for typical HIV-associated oral lesions in 29% (40 patients) with a propor-tion of 9% (13 patients) for linear gingival erythema (LGE), 3,6% (5 patients) for acute necrotizing and ulcerative gingivitis (ANUG) or periodontitis (ANUP), 7% (10 patients) for oral candidiasis and 3,6% (5 patients) for oral hairy leucoplakia (OHL). Single other lesions were seen for aphthous ulcers (2 patients), Kaposi`s sarcoma (1 patient), oral condylomata accuminata (2 patients) and ART-associated hyperpigmentation (2 patients). The overall distribution of relevant oral findings are shown in Figure 1.

The association for different oral manifestation with CD4-count or viral load is listed in Table 3 and 4. Significant associations were found for oral candidiasis ($p = 0.002$) and necrotizing ulcerative diseases ($p = 0.049$) with low CD4-count but no significant association was found with viral load. Furthermore there was no association of different oral lesion with gender,

Table 3. Lesion prevalence by CD4-count.

		CD4+ lymphocytes (cells/µl)			
Lesion	**Total No (%)**	**<200 (n = 39) No (%)**	**200-500 (n = 57) No (%)**	**>500 (n = 38) No (%)**	**p-value**
Any oral lesion	119 (86)	35 (92)	48 (81)	34 (87)	0.32
Any periodontal lesion	106 (76)	30 (79)	45 (75)	31 (80)	0.82
Gingivitis	39 (28)	8 (21)	16 (41)	15 (38)	0.11
Periodontitis	42 (30)	12 (31)	21 (48)	9 (21)	0.39
LGE	13 (9)	4 (31)	4 (31)	5 (38)	0.69
ANUG/ANUP	5 (3.6)	4 (80)	1 (20)	-	**0.04**
Candidiasis	10 (7)	8 (80)	1 (10)	1 (10)	**< 0.01**
OHL	5 (3.6)	3 (60)	2 (40)	-	0.24

Table 4. Lesion prevalence by HIV-RNA.

	HIV-RNA (copies/ml)		
Lesion	**<1000 (n = 94) No (%)**	**>1000 (n = 42) No (%)**	**p-value**
Any oral lesion	83 (70)	36 (30)	0.79
Any periodontal lesion	79 (74)	28 (26)	0.89
Gingivitis	27 (69)	12 (31)	0.98
Periodontitis	31 (74)	11 (26)	0.43
LGE	12 (92)	1 (8)	0.06
ANUG/ANUP	2 (40)	3 (60)	0.17
Candidiasis	6 (60)	4 (40)	0.52
OHL	3 (60)	2 (40)	0.66

ANUG/ANUP, acute necrotizing ulcerative gingivitis/periodontitis; LGE, Lineal gingival erythema, OHL, oral hairy leucoplakia

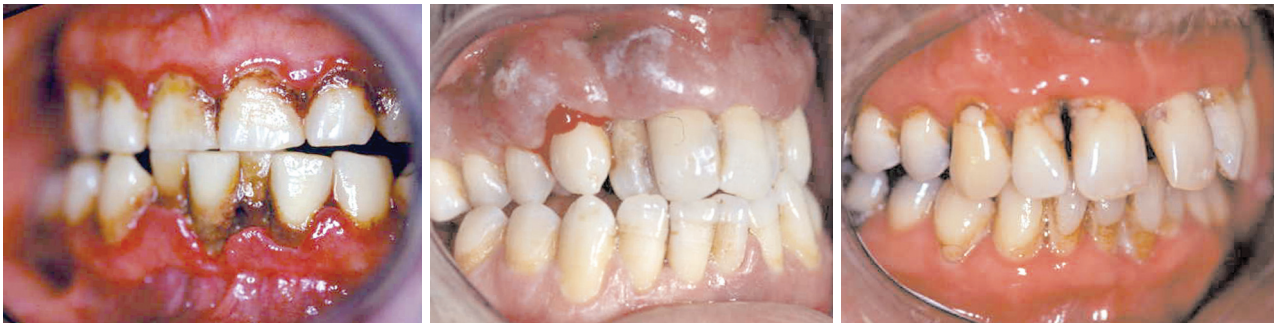

Fig. 1. Oral HIV-associated periodontal lesions presenting as (a) linear gingival erythema (LGE), characterized by a marginal band of intense erythema, (b) acute necrotizing ulcerative gingivitis (ANUG), characterized by necrosis of the interdental papilla and marginal gingiva with, (c) former necrotizing ulcerative periodontitis (NUP) with residual interdental destruction, pocket depth and attachment loss.

Table 5. Plaque Index (PI) and periodontal disease.

	Plaque Index (PI)		
Periodontal lesions	**Grade 1+2**	**Grade 3+4**	**p-value**
Yes	40	66	**0.01**
No	23	10	

Table 6. Papillary bleeding index (PBI) and CD4 count/HIV-RNA.

	Papillary bleeding index (PBI)		
	Grade 0+1	**Grade 2-4**	**p-value**
CD4+ lymphocytes (cells/µl)			
- <200	17	21	**0.03**
- 200-500	34	25	
- >500	32	7	
HIV-RNA (copies/ml):			
- <1000	41	20	0.14
- >1000	41	34	

smoking habits, ethnic origin or treatment with antiretroviral substances (data not shown).

Periodontal disease was significantly associated with an elevated plaque index ($p = 0.01$) counting oral plaque formation as a parameter for oral hygiene (Table 5). Furthermore examination of the papillary bleeding index (PBI) as a parameter for periodontal inflammation was significantly more often associated in patients with moderate or severe immunosuppression (CD4 count <500 cells/µl) than in patients with less advanced CD4 depletion ($p = 0.03$). There was no association for PBI and viral load (Table 6).

Discussion

Before the era of HAART, lesions such as oral candidiasis and OHL were frequently found in patients with HIV. A descriptive analysis of 14 studies from Western Europe or America found oral candidiasis in 12-66% of subjects, OHL in 5-43% cases and periodontal diseases in 0-50% of cases [14]. After the initiation of HAART few studies reported a decline of the prevalence of these oral diseases, ranging for oral candidiasis between 0-17%, for OHL between 0-11% and for periodontal ulcerative diseases between 1.6-4.1% [15-18]. In a study by Eyeson et al the prevalence for HIV-specific oral lesions for patients on ART was 51% with a proportion of 4.9% for oral candidiasis, 9.9% for OHL, 6% for LGE and 9.9% for ulcerative periodontal diseases [19]. A shift of oral manifestations from classical HIV-related lesions to periodontal lesions was assumed.

In our group of 139 HIV positive individuals we found comparable data to the published studies listed above with prevalence for HIV-specific oral lesions of 30%. We found a proportion of 7% for oral candidiasis, 3.6% for oral hairy leucoplakia (OHL), 9% for linear gingival erythema (LGE) and 3.6 % for acute necrotizing and ulcerative gingivitis (ANUG) or periodontitis (ANUP). Furthermore in 6 additional pa-

tients with pronounced interdental destruction, pocket depth and attachment loss a former necrotizing ulcerative disease was assumed. These data underscores a reduction of former typical HIV-related lesions of the pre-HAART era such as oral candidiasis or OHL whereas HIV-specific periodontal manifestations as LGE and NUG/NUP was comparable frequently seen.

This trend is underlined by the finding of a high prevalence for overall periodontal disease (76%) with most patients presenting chronic gingivitis or chronic periodontitis. A differentiation between HIV-associated and conventional periodontitis as this is described in other studies [20] was not per-formed in our cohort. Clinical signs of HIV-associated periodontitis are characterized by more pro-found gingival bleeding, pocket depth and attachment loss but especially at earlier stages a clear discrimination is difficult to assess. An HIV-positive person might have a conventional periodonti-tis and in addition HIV-related periodontal diseases. Among the non-immune-suppressed general population in Germany the prevalence of periodontal disease for people older than 35 years is about 75% [21], which equals the amount of periodontal lesions we found in our cohort. Nevertheless, pronounced periodontal inflammation as indicated by the elevated papillary bleeding index (PBI) was significantly associated with moderate or severe immunosuppression compared to less immunocompromised individuals in our cohort, which might account for HIV-dependent periodontal disease. We assume that periodontal inflammation is a risk factor for periodontitis and consequently LGE and NUG/NUP and other published studies have also described such an association of advanced immunosuppression with periodontal disease [22, 23]. In addition a clear association of patients presenting acute necrotizing ulcerative disease with severely suppressed CD4-counts was seen, underlining the risk of immunosuppression and periodontal inflammation with advanced periodontal manifestation.

Furthermore we found an association for periodontal disease with the amount and density of gingival plaque formation counting oral hygiene as an additional known risk factor for periodontitis and gingivitis.

In conclusion we found a high prevalence of periodontal diseases compared to former known typical HIV-specific oral lesions. Thus, our data may indicate a shift in oral disease after wide-spread use of HAART. Lack of oral hygiene determined by plaque formation and reduced CD4-counts with pronounced periodontal inflammation can be seen as risk factors for periodontal diseases in HIV-positive patients. Therefore pronounced periodontal disease might be an indicator for advanced disease. As oral lesions are often entry for pathogenic microbes leading to other focal or disseminated inflammatory diseases predominantly in patients with advanced immunosuppression, special care is needed. This study was performed cross-sectionally at a general HIV-out-patient-unit compared to other studies of specialized dental clinics. Thus, the findings may show clinical reality of a representative general HIV-population, as patient inclusion was non-selective and random. Overall high prevalence of manifestations underlines the importance of oral examination for the general practitioner and visits by oral specialists should become a routine procedure in HIV-patients care.

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